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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/500,585 | 10/21/2004 | Xinghai Chen | 1392/10/12 PCT/US | 5246 |
| 25297 7590 10/16/2007 JENKINS, WILSON, TAYLOR & HUNT, P. A. 3100 TOWER BLVD., Suite 1200 DURHAM, NC 27707 | | | EXAMINER SMITH, CAROLYN L | |
| | | | ART UNIT 1631 | PAPER NUMBER |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/500,585

Applicant(s)

CHEN ET AL.

Examiner

Carolyn L. Smith

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 July 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-30 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-30 is/are rejected.
- 7) ☒ Claim(s) 28 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 30 June 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date <u>See Continuation Sheet</u> . | 6) <input type="checkbox"/> Other: _____ |

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date
:10132004,04132005,05232005,05212007.

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DETAILED ACTION

Applicant's election of Specie E (a parameter that is a genotype), filed 7/30/07, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Drawings, filed 6/30/04, are accepted by the Examiner.

Claims herein under examination are 1-30.

Claim Objections

Claim 28 is objected to because of the following informality: Claim 28 (line 9) recites the phrase "the sample that were" which does not make grammatical sense. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-30 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

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Under the Interim Guidelines for Examination of Patent Applications for Patent Subject Matter Eligibility (published in the O.G. notice (1300 OG 142) on 11/22/2005) a method that does not result in a physical transformation of matter MAY be statutory where it recites a concrete, tangible and useful result; i.e. a practical application.

In the instant case, the claims are drawn to a method, a computer readable medium comprising a method, a system comprising a method, and a computer system with modules that comprise a method. A statutory process must include a step of a physical transformation, or produce a useful, concrete, and tangible result (State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998), AT&T Corp. v. Excel Communications Inc. (CAFC 50 USPQ2d 1447 (1999))). In the instant claims, there is no step of physical transformation, thus the Examiner must determine if the instant claims include a useful, concrete, and tangible result.

In determining if the claimed subject matter produces a useful, concrete, and tangible result, the Examiner must determine each standard individually. For a claim to be "useful," the claim must produce a result that is specific and substantial. For a claim to be "concrete," the process must have a result that is reproducible. For a claim to be "tangible," the process must produce a real world result. Furthermore, the claims must be limited only to statutory embodiments.

In the instant case, claims 1-30 do not produce a tangible result. As currently recited, the methods in the claims may take place entirely within the confines of a computer or human mind without any communication to the outside world. A tangible requirement requires that the claim must set forth a practical application of the computational steps to produce a real-world result.

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Because the claims do not recite communication of a result in a tangible form to one performing the method, the claims are not statutory. This rejection could be overcome by amending the claims to recite that a result of the method is outputted to a display or a memory, or by including a physical transformation (provided there is adequate written support in the originally filed application).

Claim Rejections – 35 U.S.C. 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in *In re Wands*, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of the skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

LACK OF ENABLEMENT

Claims 1-30 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the

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art to which it pertains, or with which it is most nearly connected, to make and/or use the claimed invention.

It is well known that the Human Genome Project has revealed that the number of human genes is in the range of 30,000. Even this number is controversial. Applicant's invention is directed to the assembling a distribution of gene expression level measurements, calculating a significance score, selecting measurements based on the score, comparing parameters between selected and non-selected measurements, and determining at least one parameter from the selected gene expression measurements that is not present in the non-selected gene expression measurements in order to infer function of one or more genes. It is also well known that a multitude of polymorphisms exists in human genes caused by environmental factors such as chemicals or cosmic rays. These complications result in an unpredictable length and difficulty in a research project that simply compares gene expression measurements between selected and non-selected gene expression level measurements to infer a function of genes. It is known that some genetic sequences are correlated with particular diseased individuals, but that each of these sequences was elucidated by lengthy research projects where the findings of the gene sequence was difficult and unpredictable. Thus, the simply comparing parameters of selected and non-selected gene expression levels as currently stated in the instant claims may not predictably result in gene function inference. It is not known whether the parameters being compared are even related to another, or if the genetic expression samples are even related to each other. It is possible that some of the gene expression measurements are "significant" due to experimental noise in the data or because they are from completely different organisms. Comparing the expression level data may find differences in the data, but one of skill in the art would not be

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able to infer the function of the gene without considerable additional research and even then such function determination is unpredictable. The publication of Doberstein et al. is cited regarding paragraphs 0003-0008 to support the numerous difficulties involved in relating gene sequences to other factors even utilizing modern bioinformatics tools. It is also noted one skilled in the art would not scientifically conclude that simply comparing genotypes results in inferring the function of a gene. Because of the undue experimentation necessary, the nature of the invention, the state of the prior art, the relative skill of those in the art, the unpredictability of the art, and the breadth of the claims, the instant claims are rejected due to a lack of enablement.

Claims Rejected Under 35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

The preamble of claim 1 is directed to inferring a function of one or more genes while the body of the claim does not mention any such inferring. Therefore, it is not clear if the preamble is intended to limit the method and what relationship is intended between the preamble and the methods steps. This issue is also present in claims 10, 18, 27, and 29. Clarification of this issue via clearer claim wording is requested. Claims 2-9, 11-17, 19-26, and 30 are also objected to due to their direct or indirect dependency from claims 1, 10, 18, and 29.

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Claims 1 (line 8), 10 (line 9), 18 (line 9), 27 (line 14), and 29 (line 6) recite the term “its” which lacks clarity. It is unclear if “its” is referring to “at least one gene expression level measurement” or “distribution” in claims 1, 10, 18, and 27. In claim 29, it is unclear to which particular “data point” or “data points” is being referred. Clarification of this issue via clearer claim wording is requested. Claims 2-9, 11-17, 19-26, and 30 are also objected to due to their direct or indirect dependency from claims 1, 10, 18, and 29.

Claims 1 (lines 9-10), 10 (lines 10-11), 18 (lines 10-11), and 27 (lines 15-16) recite “said at least one parameter” of selected and non-selected gene expression level measurements. It is unclear if these parameters are supposed to be the same for the selected and non-selected measurements or if they can vary. If they can vary, then it is unclear what kind of comparison can be made. A similar issue is present in claim 29. Clarification of this issue via clearer claim wording is requested. Claims 2-9, 11-17, 19-26, and 30 are also objected to due to their direct or indirect dependency from claims 1, 10, 18, and 29.

Claims 2 (line 1), 3 (lines 2-3), 5 (lines 1-2), 6 (lines 1-3), 8 (lines 1-3), 11, 12, 14, 15, 17, 19, 20, 22, 23, and 25 recite the phrases “said gene expression level measurements”, “said at least one gene expression level measurement”, and “the expression level measurements” which lack clear antecedent basis as it is unclear if the measurements are referring to those from selected, non-selected, or both types. Clarification of this issue via clearer claim wording is requested.

Claim 18 (line 1) recites “the method” which lacks clear antecedent basis as there is no previous mention of a method. Clarification of this issue via clearer claim wording is requested. Claims 19-26 are also objected to due to their direct or indirect dependency from claim 18.

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Claim 28 (line 6) recites “calculating a score” which is vague and indefinite. It is unclear if a score is calculated for each expression level measurement or if a single score is calculated for the group of measurements. Clarification of this issue via clearer claim wording is requested.

Claim 29 (line 1) recites “the function” which lacks clear antecedent basis as there is no previous mention of a function. Clarification of this issue via clearer claim wording is requested.

Claim 30 is also objected to due to its dependency from claim 29.

Claim Rejections – 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-3, 6-12, 15-20, and 23-30 are rejected under 35 U.S.C. 102(a) as being anticipated by Van der Laan et al. (Biostatistics, December 2001, Vol. 2(4): pages 445-461).

Van der Laan et al. disclose a method of identifying genes and adding function annotations (inferring function) to genes from gene databases (abstract). Van der Laan et al. disclose using gene expression distribution with applied parameters (abstract). Van der Laan et al. disclose finding means and covariances (abstract) which represent scores with significance. Van der Laan et al. disclose selecting a target subset of genes that are of biological interest based on statistics (scores) (abstract). Van der Laan et al. disclose estimating subsets of genes as well

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as their distribution and relevant measures (abstract). Van der Laan et al. disclose using clustering of subsets (abstract) which represents a comparison of subsets, target (selected) and not. Van der Laan et al. disclose sample means are within distance of the population mean and covariance (abstract) which represents a predefined distance. Van der Laan et al. disclose using a leukemia data set (abstract) which represents a genotype. Van der Laan et al. disclose comparing gene expression profiles across cells at different stages, in distinct pathological states, under different experimental conditions (page 446, second paragraph). Van der Laan et al. disclose comparing expression profiles from healthy cells and cancerous cells and learning which genes are over or under-expressed and studying differential gene expression that is associated with tumor suppression (page 446, second paragraph) which represents determining one parameter from selected genes not present in non-selected gene expression level measurements as well as a sorting of significant scores. Van der Laan et al. disclose searching for genes that are differentially expressed compared to a control and groups of genes that are substantially correlated with each other (page 447, second paragraph). Van der Laan et al. disclose only including genes closest to cluster centers (page 447, fifth paragraph) which represents a sorting based on significant scores of overlapped versus non-overlapped parameters. Van der Laan et al. disclose simulations (page 456, first paragraph) and methodology and software to handle such data (page 460, second paragraph) which represents a system and computer readable medium. Van der Laan et al. disclose use of an algorithm and models (page 460, fourth paragraph) and displayed results (Figure 1, page 457 and Figure 2, page 459).

Thus, Van der Laan et al. anticipate the limitations in claims 1-3, 6-12, 15-20, and 23-30.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. (e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van der Laan et al. (Biostatistics, December 2001, Vol. 2(4): pages 445-461) in view of Zhao et al. (US 2003/0219797).

Van der Laan et al. describe the limitations of instant claims 1-3, 6-12, 15-20, and 23-30 as described in the 35 USC 102 rejection above. Van der Laan et al. do not describe that the significance score is a z-score or that the z-score is greater than 3 and less than -3 (instant claims 4-5, 13-14, and 21-22).

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Zhao et al. describe statistically analyzing large data arrays and using a significant z-score of 4.8 or higher (title, 0211, 0213, 0222) which is a significant z-score greater than 3, as stated in instant claims 4-5, 13-14, and 21-22.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use significant z-score values in the method of Van der Laan et al. where the motivation would have been to determine the goodness of fit between data by evaluating the statistical significance of the fit in order to extract useful and reliable information out of large data sets, as stated by Zhao et al. (abstract, 0003, 0017).

Thus, Van der Laan et al., in view of Zhao et al., make obvious the instant invention.

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR §1.6(d)). The Central Fax Center number for official correspondence is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carolyn Smith, whose telephone number is (571) 272-0721. The examiner can normally be reached Monday through Thursday from 8 A.M. to 6:30 P.M.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran, can be reached on (571) 272-0720.

October 1, 2007

/Carolyn Smith/
Primary Examiner
AU 1631